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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,739	03/14/2002	Masayuki Amagai	201487/1070	5390

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,739	AMAGAI ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,12 and 14* is/are rejected.

7)☒ Claim(s) *13,15 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed 3/25/05 have been entered. Claims 2-8, and 19-23 have been canceled. Claims 11-16 are pending in the application and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 3/25/05 response would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 12, 14, stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record and following.

In the 3/25/05 response, Applicants argued what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail, and submitted an exhibit showing the listing of titles of over 500 journal articles retrieved in a single search using key words "homozygous knockout mouse".

In response, the Federal Circuit has acknowledged, "A SPECIFICATION NEED NOT DISCLOSE WHAT IS WELL KNOWN IN THE ART. SEE, E.G., HYBRITECH INC. V. MONOCLONAL ANTIBODIES, INC., 802 F.2D 1367, 1385, 231 USPQ 81, 94 (FED. CIR. 1986)". And further pointed out "HOWEVER, THAT GENERAL, OFT-REPEATED STATEMENT IS MERELY A RULE OF SUPPLEMENTATION, NOT A SUBSTITUTE FOR A BASIC ENABLING DISCLOSURE" (Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 CAFC 1997). Here, the issue is whether the genus of knockout *donor* mice suitable for instantly claimed process is well-known in the art, and whether the immune cells are readily available for establishing a genus of various autoimmune diseases. To this end, the specification fails to point out which mice in the art or in the 500+ list are suitable for use in the claimed invention, it fails to even name any other knockout mice beyond Dsg3-/- that may be suitable for practicing the instant invention, it fails to describe sufficient relevant characteristics of immune cells of any other knockout mice, and it fails to reduce to practice of making another autoimmune disease model, such that a person skilled in the art would recognize that the inventor had possession of the claimed genus. Since the genus of autoantigen knockout mice and characteristics of the immune cells of these mice are critical starting materials for practicing the instantly claimed invention, what is known in the art cannot substitute for a basic description of the full scope of the claimed invention.

With regard to the more than 500 publications, the applicants failed to point out which of them are autoantigen knockout mice, which immune cells could be used for establishing a type of autoimmune disease. Applicants failed to point out even one other homozygous knockout mouse whose knockout gene encodes an autoantigen, and

whose immune cells are capable of inducing a type of autoimmune disease upon adoptive transfer, let along a genus of knockout mice and suitable immune cells. Thus neither the specification nor the later submitted exhibit provides adequate description for the claimed invention. Applicants are reminded "LAW REQUIRES THAT THE DISCLOSURE IN APPLICATION SHALL INFORM THOSE SKILLED IN THE ART HOW TO USE APPLICANT'S ALLEGED DISCOVERY, NOT HOW TO FIND OUT HOW TO USE IT FOR THEMSELVES" *In re Gardner* 166 USPQ 138 (CCPA) 1970 Here, by submitting the titles of more than 500 publications, the applicants apparently challenged the skilled artisans to search through the literatures and to carry out undue experimentation identifying autoantigen knockout mice with immune cells that can induce an autoimmune disease. Apparently, applicants are asking the skilled artisans to find out for themselves how to use the applicants' alleged discovery. Thus, it is maintained that the specification fails to provide an adequate written description for the claimed invention.

Applicants then argued the genotype and phenotype of the donor mice are readily identifiable through well-known methods such as PCR.

In response, as indicated *supra*, even if searching through the more than 500 publications and performing PCR on potential candidate mice are considered as routine experimentation, further characterizing the immune cells of these mice, and looking for those that are capable of initiating and sustaining an autoimmune disease would require enormous amount of work, and all these searching and testing may or may NOT find a mouse line that is capable of being the starting material of instantly claimed invention, i.e. the results of the above experimentation is unpredictable. Accordingly, it is

concluded the specification fails to provide an adequate written description for the starting materials used in the claimed method.

Applicants went on to argue a skilled practitioner having an interest in an autoimmune disease will have investigated the initiation and sustaining mechanism of an autoimmune disease, thus the written description does not require the importance of the knockout antigen.

In response, the importance of the knockout antigen was brought up in the previous Office action (see e.g. page 7) because certain autoimmune disease is initiated by combined effects of multiple auto-antigens. Thus, knocking out one type of auto-antigen may not be sufficient to obtain immune cells that are capable of reproducibly generating the phenotype of the desired autoimmune disease (See the teachings of *Schloot et al* and *Clement et al*, pages 10-11 of the previous Office action).

Accordingly, for reasons of record and set forth *supra*, the rejection stands.

Claims 11, 12, 14 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record and following.

Applicants argued that the common attributes or characteristics of a donor mouse of the claimed invention are specifically taught in the present application, and the usefulness of the claimed invention is in no way limited to the exemplary pemphigus vulgaris model, but has wide applicability as a method to produce an autoimmue disease model. Applicants then submitted a post-filing date publication by *Xiao et al* (J Clin Invest 2002 Oct.;110:955-63) as supporting evidence stating "*Xiao substantiates*

the sufficiency of the disclosure of the present application". Applicants also submitted the publication of *Aratani et al* (Infect Immunity 1999 Apr;67:1828-36) as support for the availability of autoantigen knockout mice because the MPO knockout mice used by *Xiao et al* were the 16th generation progeny of a backcross mouse line originally made by *Aratani et al*.

As an initial matter, it is noted *Aratani et al* was published after the priority date of the instant application, thus the MPO mouse used for generating the MPO-/- mouse used by *Xiao et al* was not available at the time the instant priority date. Moreover, the MPO knockout mice created by *Aratani et al* were fertile, thus the mice used by *Xiao et al* require to be backcrossed into C57BL/6J, and undergone multi-generation breeding. Thus the mice used by *Xiao et al* were not available to the public until long after the instant priority date.

As to the mouse model disclosed by *Xiao et al*, it is noted although the experimental design bears similarities with what is instantly claimed, the outcome was not what is now claimed, i.e. many features of the mice do not meet instant claim limitation, and the mouse model do not appear to be an autoimmune one but an immune complex disease-model. This could be seen from the title of the publication, "the antineutrophil cytoplasmic autoantibodies specific for MPO cause glomerulonehritis and vasculitis in mice". *Xiao et al* confirmed the role of the MPO-autoantibody in the induction of the glomerulonephritis and vasculitis, but not the role of the immune cells (splenocytes) from the MPO-knockout mice. It should be noted the "autoantibody" was exogenously administered to the recipient mouse, not produced by the recipient mouse

as recited in claim 11. *Xiao et al* reported, immunofluorescence microscopy demonstrated that all groups of *Rag2-/-* mice, which received antigen-specific anti-MPO immune cells, or non-specific anti-BSA immune cells, or even normal control splenocytes, developed similar mild to moderate granular glomerular localization of mouse Ig's. They reported "GLOMERULAR STAINING FOR MPO WAS NO DIFFERENT IN MICE THAT RECEIVED ANTI-MPO SPLENOCYTES COMPARED WITH THOSE THAT RECEIVED ANTI-BSA OR CONTROL SPLENOCYTES" (column 2, page 958, emphasis added). *Xiao et al* went on to teach, "THIS LOW TO MODERATE LEVEL OF GLOMERULAR IMMUNE COMPLEX LOCALIZATION WAS THE SAME IN INTENSITY AND COMPOSITION IN MICE IRRESPECTIVE OF THE TRANSFER OF ANTI-MPO, ANTI-BSA OR CONTROL SPENOCYTES". As to the mechanism, *Xiao et al* admitted, "THE BASIS FOR THIS IMMUNE COMPLEX GLOMERULONEPHRITIS IS UNKNOWN" (emphasis added). Thus, the nephritis induced by adoptive transferring immune cells of MPO-/- mice as disclosed by *Xiao et al* was characterized as "immune complex glomerulonephritis", not an autoimmune one. *Xiao et al* went on to speculate, "INDUCTION OF AN AUTOIMMUNE RESPONSE REMAINS A POSSIBILITY". However, at the time of publication, they failed to detect any autoantibody from cell extracts of the recipient mice (column 2, page 961). In an effort to distinguish the role of T and B lymphocytes comprised in the transferred splenocytes, *Xiao et al* administered anti-MPO antibodies in place of splenocytes, and found specific induction of the kidney lesion. They thus went on to conclude "THIS DEMONSTRATES THAT ANTI-MPO IGG CAUSES GLOMERULAR NECROSIS AND CRESCENTS IN THE ABSENCE OF ANTIGEN-SPECIFIC T AND B LYMPHOCYTES IN RAG2-/- MICE AND IN THE PRESENCE OF A COMPETENT IMMUNE SYSTEM IN WT B6 MICE" (3rd paragraph, page 962, emphasis added). Since the so called anti-MPO autoantibody was artificially administered into the recipient mice, the kidney lesion in

mice disclosed by *Xiao et al* was neither mediated by autoantibodies nor mediated by autoantigen-specific T cells. Thus the mice of *Xiao et al* do not meet instant claim limitation, which require, "*producing a mouse recipient that produces an antibody reactive to the antigen protein for an autoimmune disease and/or has activated T cells reactive to the antigen protein*". Accordingly, the *Xiao* reference fails to substantiate the sufficiency of the disclosure of the present application, but confirms the position of the Office: it would have required further development of the art, and thus undue experimentation for the skilled in the art to produce a genus of autoimmune disease-models as claimed at the time of the instant priority date.

Accordingly, for reasons of record and set forth *supra*, the instant disclosure fails to meet the statutory enablement requirement.

Claim Objections

Claims 13, 15, 16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations into the base claim.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Ram R. Shukla** can be reached on 571-272-0735. The fax numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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June 7, 2005